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ART UNIT	PAPER NUMBER
1652	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/426,548	Applicant(s) Robbins et al.
	Examiner Joseph Woitach	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-8 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-8 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5,6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Claim Objections

Claim 1 is objected to because of the following informalities: The claims as written do not comply with the sequence rules 37C.F.R. 1.821(d). When claims discuss a sequence that is set forth in the "Sequence Listing", reference to the sequence must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 8 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 8 is a directed to a 'system' comprising cells. The specification does not define what is specifically meant by a 'system', but from the disclosure it appears that a transgenic animal is intended, and not just cells. In this case, claim 8 encompasses any transgenic organism, including a human being. Changing the claim to read a transgenic non-human transgenic model would obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published on December 12, 1999 in the Federal Register at Volume 64, Number 244, pp.71427-71440.

Claim 8 is drawn to a transgenic model system for colorectal cancer comprising cells expressing the variant human MLH1 or MSH2 gene of claim 1. Claim 8 encompasses the expression of the gene variants in a cell line and an animal, or alternatively, inserting the specific genetic alteration through the use of homologous recombination. The specification teaches general methodology on how to create a cell line from a patient who has the desired genetic variant, however, a cell from a patient would not contain a transgene and thus would not constitute a transgenic model because only an endogenous variant is expressed. General methodology and several references are recited for the creation of transgenic and knock-out animals. However, there is no reduction to practice of any cell line, nor transgenic animal in the

specification, nor the use of the construct to create an ES cell which could give rise to a transgenic mouse or any other animal. The general methodology taught in the specification to create and select an animal depends on the ability to create and identify an ES cell which has undergone homologous recombination. The specification is silent with respect to a source of these cells for the creation of transgenic animals other than that for the mouse, and with respect to methods for the use of cells other than ES cells to create said transgenic non-human mammal. Finally, for the realization of the model system the expression of the genetic variants must produce a cell or animal which can serve as a model for colorectal cancer. The specification is silent with respect to the expected phenotype one would expect by expressing these genetic variants and is absent of an actual reduction to practice to demonstrate that expression would actually produce a phenotype.

In analyzing whether the written description requirement is met for genus claims, it is first determined were a representative number of species have been described by the complete structure. (It is not realistic to expect that the "complete structure" of a cell or mouse, or any other animal could be described. Therefore the inquiry required by this portion of the written description guidelines is interpret to be whether the phenotypic consequences of altering a the genotype have been described). In this case, the few disclosed embodiments are not representative of the enormous number of products claimed. The claims encompass any transgenic model system which could serve as a model system, however, there is no reduction to practice of any embodiment. While a final expected phenotype would be the development of colorectal in an

animal model, there are no examples in the specification or in the art of record that demonstrate that expression of these genes alone would result in the expected phenotype. For example in Reitmair *et al.*, the MSH2 deficient mice produce lymphoid tumors not colorectal cancer. Finally, there is no reduction to practice of the creation of any cell line which contains the genetic variant, nor is there a description of an expected phenotype of these cells, nor how these cells would serve as a model system. While several preferred embodiments have been described for prophetic model systems in the specification, the number of species represented by the many permutations of type of animal for the animal model or origin of the cell, type of promoter, level of expression and resulting phenotypes represent many thousand of species.

Next, it is to be determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of expression of a heterologous gene can not be predicted. This is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression or disruption of a gene in different species of transgenic non-human animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). Further, some genes have been designated 'non-essential' because of their ability to be knocked-out in a mouse model and still

produce viable healthy animals, but it well known in the art that an animal model in one species may not always be representative of a phenotype produced in another. This is the primary reason that various species of animals are used as model systems in order to more closely mirror the desired phenotype or disease progression. Specifically with respect to MSH2, Reitmair *et al.* teach that expression of a gene associated with colorectal cancer in humans produce lymphoid tumors in a mouse model. The specification has not clearly demonstrated or described a method to determine the empirical nature of genetics as it varies among species, in particular the effect of knocking-out a gene by insertion of an expression cassette. The limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genus recited in the claims at the time of the application was filed. Thus the Applicant was not in possession of the genus of all transgenic animals which contain a polynucleotide comprising the recited expression cassette, and is concluded that the written description requirement is not satisfied for the claimed genus.

Enablement

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to any transgenic model system for colorectal cancer comprising cells expressing the variant MLH1 or MSH2 of claim 1.

Breadth of claims. The claims are broad, encompassing generation of any transgenic animal or transformed cell line expressing the genetic variants of MLH1 or MSH2.

Guidance in the specification. The specification provides general methodology for the creation of transformed cell lines and transgenic animals, however there is no reduction to practice for any of these embodiments. There is the prophetic expectation that expression of the transgene would produce a model system for colorectal cancer, however, as the discussed in the written description rejection and in Reitmair *et al.* expression of NLH an MSH gene variants may not produce a model system for colorectal cancer. Further, there is no guidance or description on the expected phenotype one would expect in the transgenic model system. Without a proper description of the expected phenotype, it is unclear how one could use the transgenic system for a model of any other disease or physiological state.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). This is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection:

Effect of Foreign GH on Growth). The observation is further supported by Mullins *et al.* (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins *et al.* state that "a given construct may react very differently from one species to another." Wall *et al.* further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 2215, first paragraph). As discussed in the section regarding guidance in the specification, even the expression of the MSH2 gene variant associated with colorectal cancer in humans did not produce a model system in the mouse. Further, the expression of the transgene produced a mouse that was 'surprisingly... viable and fertile for at least two generations' (pages 64-65; bridging paragraph), suggesting that the authors did not expect this phenotype.

Amount of experimentation necessary. Applicants have proposed a transgenic model system for colorectal system, however, because of the unpredictability of transgene, the lack of examples or a description of a means to determine a predictable phenotype, essentially all of the work required to define appropriate transgenes, develop and optimize the conditions for creation of transgenic animals has been left for others.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 1 is unclear with respect to the nucleotide of the sequences cited because they do not include a SEQ ID NO. Sequence databases indicate that there are multiple sequence listings for the human.

Claims 2 and 3 are unclear and incomplete in the recitation of 'the presence of the variant gene is indicative of a susceptibility to hereditary non-polyposis colorectal cancer' because method steps are not present that indicate which mutants correspond to a predisposition to colorectal cancer.

Claims 4 and 6 are unclear and incomplete in the recitation of 'identifying mutants in splice donor or acceptor sites' because method steps are not present that indicate the base pair changes detect would result in the claimed splice mutants.

Claim 8 is vague and indefinite in the recitation of 'system'. It is not clear if by system Applicant intends to claim just cells or an animal. Usually, the use of transgenic is reserved for the description of an animal harboring a exogenous gene, and not isolated cells or cell lines. The specification discusses animals and methods to isolate cells from transgenic animals, but isolated cells from an animal are usually called something other than transgenic

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Farrington *et al.*

Farrington *et al.* teach the exact mutants in the same patients as described in the specification (page 752; Table 1). Farrington *et al.* also teach the methods and primers to detect the described mutants (page 750; section on Genomic Sequencing).

Claims 2-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Weber *et al.*

Weber *et al.* teach a method and the appropriate primers to do genomic sequencing of MLH1 and MSH2, and detect mutations predictive of heredity nonpolyposis colorectal cancer (whole document, particularly Table 1 and 2). Further, the mutation which results in the deletion

of exon 13 in patient 817, MLH1 mutant 2, has been previously described in Liu *et al.* 1995 and Dunlap *et al.* 1997 (page 754; Table 4).

Claims 2-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Liskay *et al.*

Liskay *et al.* teach a method and the appropriate primers for the detection of mutations in MLH1 and MSH2 which are associated and predictive of heredity nonpolyposis colorectal cancer (whole document and in particular figure 1, and sequences of figures 2-5, 13-16). Liskay *et al.* teach that the mouse MLH and PMS would be useful in creating transgenic models to determine cancer risk factors (column 20; lines 10-40). Therefore, t would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention to identify variants of human MLH and MSH and create transgenic animals to study the role of these variants for their possible importance in mismatch repair and colon cancer as taught by Liskay *et al.* One having ordinary skill in the art would have been motivated to do this to determine because of the link of mutations in these genes with cancer, and further to develop transgenic animal models to study the molecular mechanisms in more detail. There would have been a reasonable expectation of success given the results of Liskay *et al.* to identify other variants of the MLH and MSH genes and attempt to express these in transgenic animals to create model systems for further study.

Thus, the claimed invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached at (703)308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

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